(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization International Bureau



PCT

(43) International Publication Date 8 March 2001 (08.03.2001)

- (51) International Patent Classification7: C07K 14/71. C12N 9/12, G06F 17/30, C12Q 1/37, A61K 38/00, G01N 33/68
- (21) International Application Number: PCT/US00/23744
- (22) International Filing Date: 30 August 2000 (30.08.2000)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data: 60/151.810 30 August 1999 (30.08.1999) US
- (63) Related by continuation (CON) or continuation-in-part (CIP) to earlier application:
 - US 60/151,810 (CIP) Filed on 30 August 1999 (30.08.1999)
- (71) Applicant (for all designated States except US): NEW YORK UNIVERSITY SCHOOL OF MEDICINE [US/US]: 550 First Avenue, New York, NY 10016 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): SCHLESSINGER, Joseph [US/US]; Apartment 9D, 37 Washington Square West. New York, NY 10011 (US). HUBBARD, Stevan, B. [US/US]; 5465 Sylvan Avenue, Riverside, NY 10471

(10) International Publication Number WO 01/16181 A3

(US) MOHAMMADI, Moosa [US/US]: Apartment 12F. 564 First Avenue, New York, NY 10016 (US).

- (74) Agent: ISACSON, John, P.: Foley & Lardner, Suite 500, 3000 K. Street, N.W., Washington, DC 20007-5109 (US).
- (81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS. LT. LU. LV. MA, MD, MG, MK, MN, MW, MX, MZ. NO. NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR. TT, TZ. UA. UG. US, UZ, VN, YU, ZA, ZW.
- (84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT. BE. CH. CY. DE, DK. ES, FI, FR, GB, GR, IE, IT. LU. MC. NL, PT. SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

with international search report

(88) Date of publication of the international search report: 24 January 2002

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

3

(54) Title: CRYSTAL STRUCTURES OF DOMAINS OF RECEPTOR PROTEIN TYROSINE KINASES AND THEIR LIGANDS

01/16181 (57) Abstract: The determination and use of three dimensional structures of receptor protein tyrosine kinases and/or their ligands are described. One particular group of such structures includes three dimensional structures of the extracellular domain of RPTKs. The three dimensional structures of RPTKs can faciliate the design and identification of modulators of RPTK function. Other such structures can include of RPTK ligands, such as stem cell factor or a fragment thereof. Modulators of RPTK function can be used to treat diseases that are mediated by inappropriate RPTK activity.

A CLASSIFICATION OF SUBJECT MATTER IPC / GOIN33/68 According to International Patter Classification (IPC) or to both national classification and IPC B. FIELDS SEARCHED Minnum documentation searched classification system fullowed by classification symbols; IPC / CL2N CO7K AGLK C12Q GGIN Documentation searched classification system fullowed by classification symbols; IPC / CL2N CO7K AGLK C12Q GGIN Documentation searched classification system fullowed by classification symbols; IPC / CL2N CO7K AGLK C12Q GGIN Documentation searched classification system fullowed by classification symbols; IPC / CL2N CO7K AGLK C12Q GGIN Documentation searched classification system fullowed by classification symbols; IPC / CL2N CO7K AGLK C12Q GGIN Documentation searched classification system fullowed by classification symbols; IPC / CL2N CO7K AGLK C12Q GGIN Documentation document. with indication, where appropriate, of the relevant passages Relevant to classification of document, with indication, where appropriate, of the relevant passages Relevant to classification of document, with indication, where appropriate, of the relevant passages Relevant to classification of document, with indication, where appropriate, of the relevant passages Relevant to classification of document, with indication, where appropriate, of the relevant passages Relevant to classification of document, with indication, where appropriate, of the relevant passages Relevant to classification of document, with indication, where appropriate, of the relevant passages Relevant to classification of the relevant passages Relevant		INTERNATIONAL SEARC	CH REPORT	Inter Shal Ap	oplication No
9. FELDS SEARCHED Minimum documentation searched (classification system informed by classification symbols) IPC 7 C12 N COFX Addition of the system information searched during the international search (name of data base and, where practical, search terms used) Electronic data base consulted during the international search (name of data base and, where practical, search terms used) EPO-Internal, BIOSIS, WPI Data C. DOCUMENTS CONSIDERED TO BE RELEVANT Category - Citation of document, with indication, where appropriate, of the relevant passages Relevant to c Y PELLEGRINI L ET AL: "The role of heparin fibroblast growth factor 2 and its high fibroblast growthathits high fibroblast growth factor 2 and its		C07K14/71 C12N9/12 G06F1	17/30 C12Q1/	37 A61	K38/00
Annuen accumentation searched (classification symbols) IPC 7 C12N C07K A61K C12Q GB1N Documentation searched other than minimum documentation to the extent that such documents are included in the helds searched Electronic data base consulted during the international search (name of data base and, where practical, search terms used) EPO-Internal, BIOSIS, WPI Data C. DOCUMENTS CONSIDERED TO BE RELEVANT Category * Classon of document, with indication, where appropriate, of the relevant passages Relevant to cite Y PELLEGRINI L ET AL: The role of heparin in the complex formation between fibroblast growth factor 2 and its high affinity receptor: Comparative modelling and biochemical studies." BIOCHEMICAL SOCIETY TRANSACTIONS, vol. 26, no. 3, August 1998 (1998-08), pages 545-549, XP000993500 665th Meeting of the Biochemical Society; Southampton, England, UK; March 31-April 2, 1998 Patent tamy members are kited in anxet. // -/ -/ -/ // -/ -/ -/ // Society; Southampton, England, UK; March 31-April 2, 1998 -/ -/ // Society; Southampton, England, UK; March 31-April 2, 1998 -/ -/ // -/ -/ -/ -/ // Socienterit adocument barbinde after the international lin	According t	o International Patent Classification (IPC) or to both national clas	ssification and IPC		
IPC 7 C12N C07K A61K C12Q G01N Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electionic data base consulted during the international search (name of data base and, where practical, search terms used) Electionic data base consulted during the international search (name of data base and, where practical, search terms used) EPO-Internal, BIOSIS, WPI Data C. DOCUMENTS CONSIDERED TO BE RELEVANT Category * Citation of document, with indication, where appropriate, of the relevant passages Relevant to citation of document, with indication, where appropriate, of the relevant passages Relevant to citation of document, with indication, where appropriate, of the relevant passages Relevant to citation of document, with indication, where appropriate, of the relevant passages Relevant to citation of document, with indication, of the relevant passages Relevant to citation of the Citation of the Biochemical Society; Southampton, England, UK; March 31-April 2, 1998 1-27, 43-51, 54-65, 56-67-86 Y Patent tamiy members are taked in ancer. -/ Impacts -/ -/ Y Patent tamiy members are taked in ancer. -/ Y Patent tamiy members are taked in ancer. -/ Y Impacts Y Patent tamiy members are taked in ancer. Y Impacts					
Electronic data base consulted during the international search (name of data base and, where practical, search terms used) EPO-Internal, BIOSIS, WPI Data C.DOCUMENTS CONSIDERED TO BE RELEVANT Category * Citation of document, with indication, where appropriate, of the relevant passages Relevant to c in the complex formation between fibroblast growth factor 2 and its high affinity receptor: Comparative modelling and biochemical studies, " BIOCHEMICAL SOCIETY TRANSACTIONS, vol. 26, no. 3, August 1998 (1998-08), pages 545-549, XP000933500 665th Meeting of the Biochemical Society; Southampton, England, UK; March 31-April 2, 1998 ISSN: 0300-5127 the whole document		ocumentation searched (classification system followed by classi C12N C07K A61K C12Q G01N	ification symbols)		
EPO-Internal, BIOSIS, WPI Data C. DOCUMENTS CONSIDERED TO BE RELEVANT Category* Citation of document, with indication, where appropriate, of the relevant passages Relevant to citation Y PELLEGRINI L ET AL: "The role of heparin in the complex formation between data finity receptor: Comparative modelling and biochemical structures." 1-27, 43-51, 56-749, XP000993500 and biochemical Societry TRANSACTIONS, vol. 26, no. 3, August 1998 (1998-08), pages 545-549, XP000993500 665th Meeting of the Biochemical Society; Southampton, England, UK; March 31-April 2, 1998 Society; Southampton, England, UK; March 31-April 2, 1998 ISSN: 0300-5127 the whole document: ** document doming the generatistic of the minemational state in the international file data or priority data categories of cited documents: *** ** document doming the generatistic of the minemational state in the international state of the authority of the minemational state in the international state in the international state in the international state of the authority of the minemational state of the international state of the authority of the minemational state of the authority o	Documenta	tion searched other than minimum documentation to the extent t	hat such documents are inclu	uded in the fields se	earched
Category* Citation of document, with indication, where appropriate, of the relevant passages Relevant to c Y PELLEGRINI L ET AL: "The role of heparin 1-27, 43-51, 54-51, 54-55, 45, 54, 74, 743-51, 54-65, 67-86 and biochemical studies." BIOCHEMICAL SOCIETY TRANSACTIONS, vol. 26, no. 3, August 1998 (1998-08), pages 545-549, XP000993500 665th Meeting of the Biochemical Society; Southampton, England, UK; March 31-April 2, 1998 15SN: 0300-5127 the whole document -/ X Further documents are listed in the continuation of box C. X Patent family members are listed in annex. **Special categories of cited documents -/ ** ** document buildhed after the international fling date of another cited to indicate and no rollifer with the special relevance the ordinate of theory underlying the international fling date of another international fling			a base and, where practical,	, search terms used	
Y PELLEGRINI L ET AL: "The role of heparin in the complex formation between fibroblast growth factor 2 and its high affinity receptor: Comparative modelling and biochemical studies." BIOCHEMICAL SOCIETY TRANSACTIONS, vol. 26, no. 3, August 1998 (1998-08), pages 545-549, XP000993360 665th Meeting of the Biochemical Society; Southampton, England, UK; March 31-April 2, 1998 ISSN: 0300-5127 the whole document 67-86 X Further documents are listed in the continuation of box C. X Patent family members are listed in annex. * document defining the general state of the at which is not considered to setablished on or after the international filling date of anion or other sponal disclosure, use, exhibition or of document bubbled do or after the international filling date of the addition of box to the sponal disclosure, use, exhibition or of document published or or after the international filling date of the addition of the profit date of the or ynemity. State of the or ynemity cannot be considered now or or more the state and discover. ** document published on or after the international filling date or on their sponal discover, use, exhibition or of comment published or or the international filling date but later than the poncity date data of anonter state document published or or the international filling date but later than the poncity date data date state document published discover an inventive step when the document is combined with one or more offer stud document is combined with one or more offer stud document is combined with one or more offer stud document state of the adval completion of the international filling date but later than the poncity date data date stud document published atternational search report 26 July 2001 Tate of mailing date but international search report 26 July 2001	C. DOCUM	ENTS CONSIDERED TO BE RELEVANT			
in the complex formation between 43-51, fibroblast growth factor 2 and its high 43-51, affinity receptor: Comparative modelling 54-65, and biochemical studies." BIOCHEMICAL SOCIETY TRANSACTIONS, vol. 26, no. 3, August 1998 (1998-08), pages 545-549, XP000993500 665th Meeting of the Biochemical Society; Southampton, England, UK; March 31-April 2, 1998 ISSN: 0300-5127 the whole document X Further documents are listed in the continuation of box C. Special categories of cited documents: A' document defining the general state of the miternational file date meeting document defining the general state of another citation or other special teason (as specified) The lare document of anticular relevance: the claimed invention cannot be considered to be of particular relevance: the claimed invention mobilised atter the international file date or the special state of another claim of another within the application but cited to establish the publication date of another claimed teason (as specified) "To alter document of particular relevance: the claimed invention mobilised at the point of the same patient item invention claimed to other special reason (as specified) Coursent published or to the international file date but atter than the point date of another claimed teason (as specified) "Coursent particular relevance: the claimed invention cannot be considered to movie an inventive site when the documents is such another such as	Category °	Citation of document, with indication, where appropriate, of the	e relevant passages		Relevant to claim No.
 ¹ Special categories of cited documents : ¹ A document defining the general state of the art which is not considered to be of particular relevance ¹ earlier document but published on or after the international filing date ¹ document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) ¹ document published prior to the international filing date but later than the priority date claimed ¹ document published prior to the international filing date but later than the priority date claimed ¹ document published prior to the international filing date but later than the priority date claimed ¹ document published prior to the international filing date but later than the priority date claimed ² document published prior to the international filing date but later than the priority date claimed ² document published prior to the international filing date but later than the priority date claimed ² document published prior to the international filing date but later than the priority date claimed ² document published prior to the international search ² document published prior to the international search ² document member of the same patent tamily ³ Date of mailing of the international search report ⁴ 2 6. 10. 01 	Y	<pre>in the complex formation betwe fibroblast growth factor 2 and affinity receptor: Comparative and biochemical studies." BIOCHEMICAL SOCIETY TRANSACTIO vol. 26, no. 3, August 1998 (19 pages 545-549, XP000993500 665th Meeting of the Biochemica Society;Southampton, England, 31-April 2, 1998 ISSN: 0300-5127</pre>	en its high modelling 998-08), al UK; March		43-51, 54-65,
 A* document defining the general state of the art which is not considered to be of particular relevance E* earlier document but published on or after the international filing date L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) C* document referring to an oral disclosure, use, exhibition or other means CP* document published prior to the international filing date but later than the priority date claimed Cate of the actual completion of the international search 26 July 2001 C* later document published after the international filing date but the art units of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is cambined with one or more other such document is combined with one or more other such document and the art. C* document published prior to the international filing date but later than the priority date claimed C* document member of the same patent tamily C* document member of the international search report 26 July 2001 			X Patent family me	embers are listed in	annex.
26 July 2001 2 6. 10. 01	A docume consid E earlier d filing d 'L docume which i citatior 'O' docume other n 'P' docume	end defining the general state of the art which is not ered to be of particular relevance locument but published on or after the international ate nt which may throw doubts on priority claim(s) or is cited to establish the publication date of another n or other special reason (as specified) ent referring to an oral disclosure, use, exhibition or neans not published prior to the international filing date but	 or provity date and r cited to understand invention "X" document of particula cannot be considere involve an inventive "Y" document of particula cannot be considere document is combin ments, such combin in the art. 	not in conflict with the the principle or theo ar relevance; the clai ed novel or cannot be step when the docu ar relevance; the clai ed to involve an invei- ed with one or more lation being obvious	e application but ny underlying the e considered to ment is taken alone med invention nitive step when the other such docu- to a person skilled
					n report
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016 VAN DER SCHAAL C.A.		nailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk	Authorized officer		

Form PCT/ISA/210 (second sheel) (July 1992)

4

INTERNATIONAL SEARCH REPORT

Inter ¹onal Application No PCI/US 00/23744

Relevant to claim No. 1-27, 43-51, 54-65, 67-86 1-27, 43-51, 54-65, 67-86
1-27, 43-51, 54-65, 67-86 1-27, 43-51, 54-65,
43-51, 54-65, 67-86 1-27, 43-51, 54-65,
43-51, 54-65,
1-27, 43-51, 54-65, 67-86
58-65
1-27, 43-51, 54-57, 67-86
58-65

4

Ŷ

,

INTERNATIONAL SEARCH REPORT

Intervision No PCT/US 00/23744

C.(Continue	ation) DOCUMENTS CONSIDERED TO BE RELEVANT	
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Ρ,Χ	PLOTNIKOV ALEXANDER N ET AL: "Crystal structures of two FGF-FGFR complexes reveal the determinants of ligand-receptor specificity." CELL, vol. 101, no. 4, 12 May 2000 (2000-05-12), pages 413-424, XP002167377 ISSN: 0092-8674	1-27, 43-51, 54-57, 67-69, 76-86
Y	the whole document	58-65, 70-75
P,X	PELLEGRINI LUCA ET AL: "Crystal structure of fibroblast growth factor receptor ectodomain bound to ligand and heparin." NATURE (LONDON), vol. 407, no. 6807, 2000, pages 1029-1034, XP002167378 ISSN: 0028-0836	1-4,8, 19-23, 43-51, 67-74,76
Ŷ	the whole document	5-7, 9-18, 24-27, 54-65, 75,77-86
Ρ,Χ	STAUBER DEBORAH J ET AL: "Structural interactions of fibroblast growth factor receptor with its ligands." PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES, vol. 97, no. 1, 4 January 2000 (2000-01-04), pages 49-54, XP002167379 Jan. 4, 2000 ISSN: 0027-8424	1-4,8, 19-23, 43-51, 67-74,76
Y	the whole document	5-7, 9-18, 24-27, 54-65, 75,77-86

4

ł

Form PCT/ISA/210 (continuation of second sheet) (July 1992)



INTERNATIONAL SEARCH REPORT

Form PCT/ISA/210 (continuation of first sheet (1)) (July 1998)

		INTERNATIONAL SEARCH REPORT	national application No. PCT/US 00/23744
	Box i	Observations wh re certain claims were found unsearchable (Continua	tion of item 1 of first sheet)
,	This Inte	ernational Search Report has not been established in respect of certain claims under Art	ticle 17(2)(a) for the following reasons:
	1. X	Claims Nos.: because they relate to subject matter not required to be searched by this Authority, nar see FURTHER INFORMATION sheet PCT/ISA/210	mely:
	2. X	Claims Nos.: 66 because they relate to parts of the International Application that do not comply with the an extent that no meaningful International Search can be carried out, specifically: see FURTHER INFORMATION sheet PCT/ISA/210	prescribed requirements to such
	3.	Claims Nos.: because they are dependent claims and are not drafted in accordance with the second	and third sentences of Rule 6.4(a).
	Box ii	Observations where unity of invention is lacking (Continuation of item 2	of first sheet)
	This Inte	ernational Searching Authority found multiple inventions in this international application, a	as follows:
		see additional sheet	
	1.	As all required additional search fees were timely paid by the applicant, this International searchable claims.	al Search Report covers all
	2.	As all searchable claims could be searched without effort justifying an additional fee, this of any additional fee.	s Authority did not invite payment
-	3.	As only some of the required additional search fees were timely paid by the applicant, th covers only those claims for which fees were paid, specifically claims Nos.:	nis International Search Report
\$ \$ \$	4. 🗶	No required additional search fees were timely paid by the applicant. Consequently, this restricted to the invention first mentioned in the claims; it is covered by claims Nos.: Claims 1-27, 43-51 and 54-86.	International Search Report is
-	Remar	c on Protest The additional search fees were acc No protest accompanied the payme	companied by the applicant's protest. Int of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

} ;

Although claim 68 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Although claims 43-51 could be considered as a mere presentation of information or a computerprogram, Rule 39.1(v and vi) PCT, the search has been carried out as far as pssible in our systematic documentation

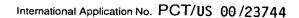
Continuation of Box I.2

Claims Nos.: 66

Present claim 66 relates to a product defined by reference to a desirable characteristic or property, namely modulation of receptor protein tyrosine kinase.

The claims cover all products having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for no such product. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the product/compound/method/apparatus by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has not been carried out.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.



FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-27 43-51 54-86

•

31

1 7 7 Crystals including an extracellular domain of a receptor tyrosine kinase and there use.

2. Claims: 28-42 52 53 87-89

Crystals comprising a receptor binding core of a stem cell factor and there use



INTERNATIONAL SEARCH REPORT

.. iormation on patent family members

Inter 2011 Application No PCT/US 00/23744

Patent document	Publication	Patent family	Publication
cited in search report	date	member(s)	date
WO 9807835 A	26-02-1998	US 5942428 A AU 733890 B AU 4160397 A EP 0931152 A JP 2001514484 T	24-08-1999 31-05-2001 06-03-1998 28-07-1999 11-09-2001

Form PCT/ISA/210 (patent family annex) (July 1992)

7

ь

•